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Tailoring Inhibition and Degradation Strategies to Chromatin Remodelers

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FOGHORN THERAPEUTICS

Foghorn Therapeutics is Focused on Chromatin Biology

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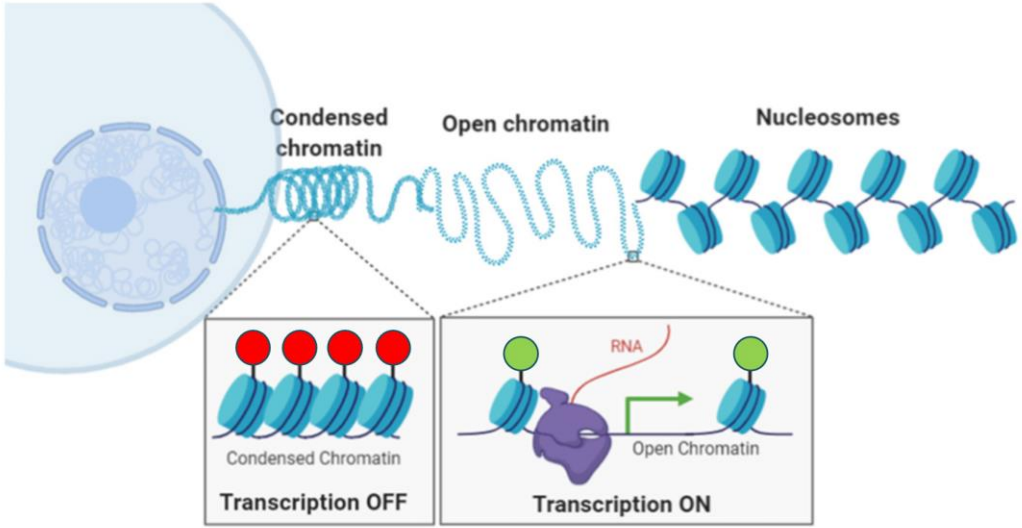
Gene expression in the right cells at the right time is critical for normal growth, development, and homeostasis



Broad Pipeline Across a Range of Targets and Modalities

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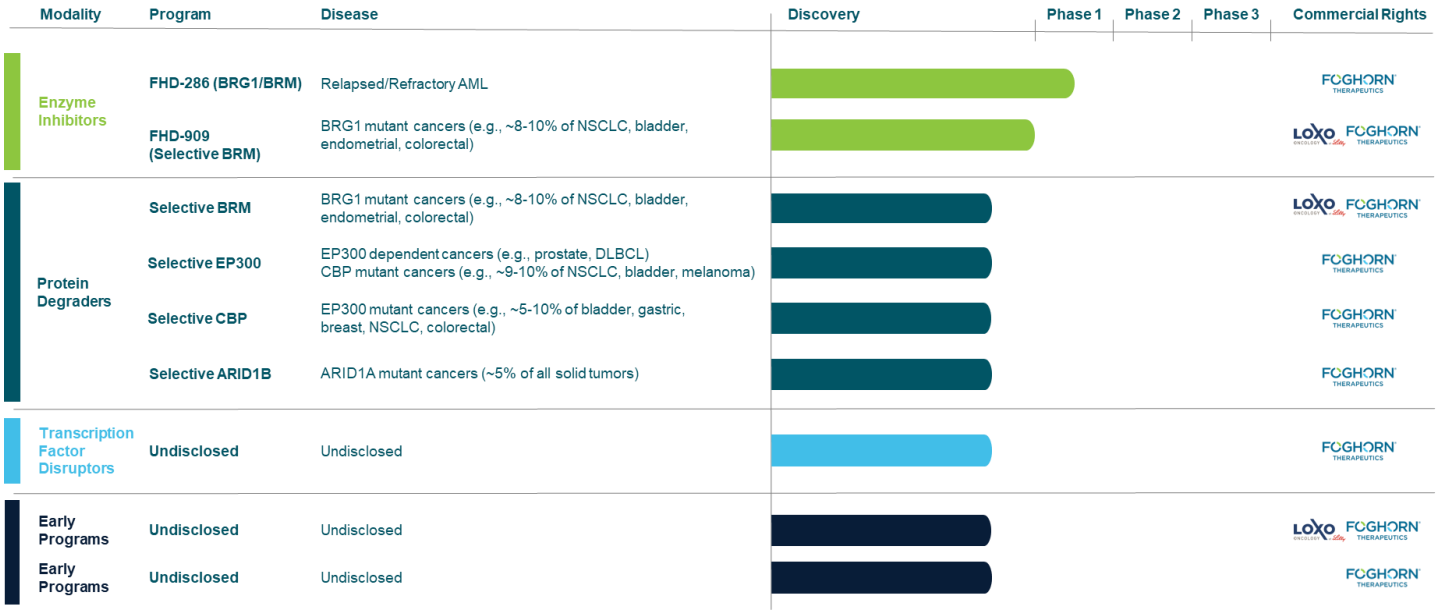

Advancing a pipeline targeting key chromatin modulators, regulators, and transcription factors involved in numerous oncology indications

Targeting BRM/BRG (SMARCA2/4): Inhibit or Degrade?

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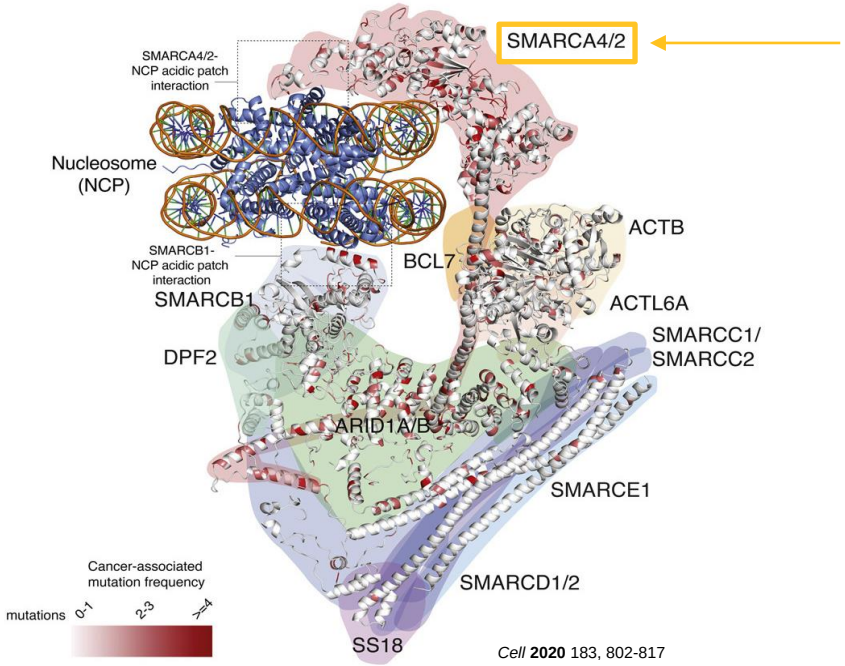
Structural model of the endogenous human BAF complex



Cell **2020** 183, 802-817

BRM/BRG1 (SMARCA2/4)

- Facilitate interaction with chromatin
- Core engine of BAF remodeling complex
- Highly homologous and mutually exclusive ATPases

Disease implications and relationships

- BRM/BRG1 frequently mutated in cancers
- Numerous oncology indications showing BRG1-deficiency
- Synthetic lethal relationship between BRM and BRG1

Drug targeting

- Several domains within BRM/BRG1 with known binders
- Known binders are not selective for BRM or BRG1

FHD-909 (LY4050784): Discovery of a Selective BRM Inhibitor for BRG1 Mutant Cancers

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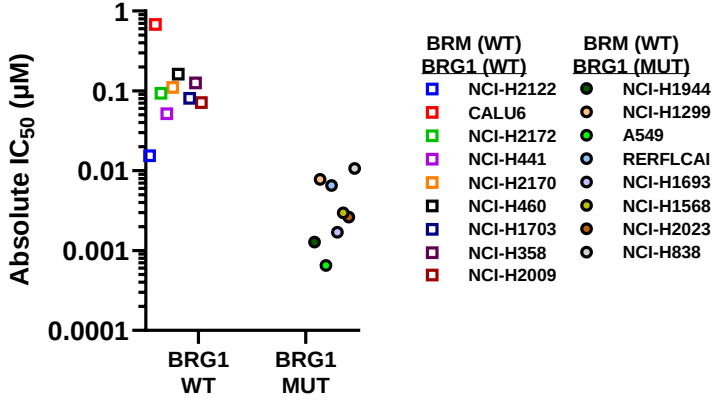
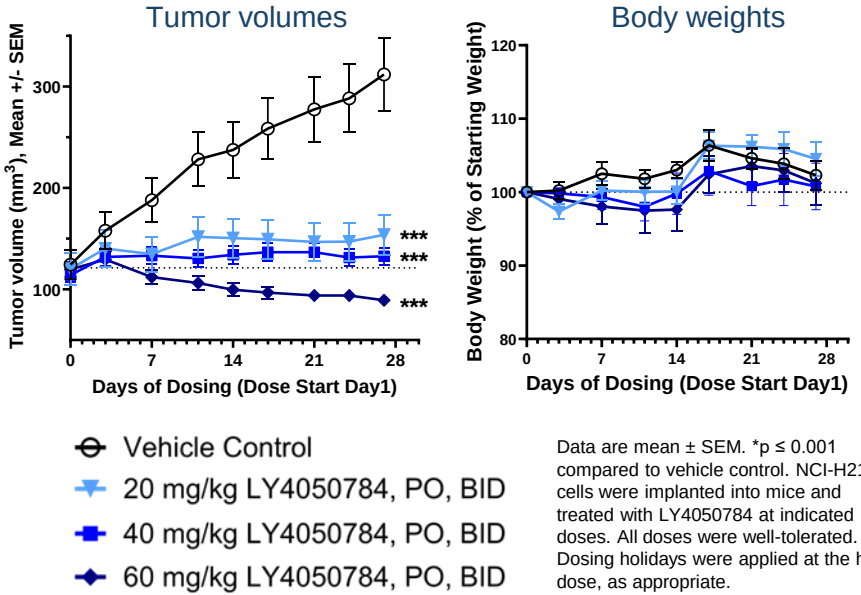
FHD-909 (LY4050784) EXHIBITS MORE POTENT ANTI-PROLIFERATIVE EFFECTS IN BRG1-MUTANT CELL LINES



	Median IC_{50} (µM)
BRG1 WT	0.0932
BRG1 MUT	0.0028
Fold diff	33x

IC_{50} values are corrected for FBS binding

ANTI-TUMOR EFFICACY IN BRG1-MUTANT NSCLC XENOGRAFT MODEL (NCI-H2126)



Data are mean ± SEM. *p ≤ 0.001 compared to vehicle control. NCI-H2126 cells were implanted into mice and treated with LY4050784 at indicated doses. All doses were well-tolerated. Dosing holidays were applied at the high dose, as appropriate.

LOXO@Lilly

Targeting ARID1B for ARID1A Mutant Cancers: Why Pursue a Degrader?

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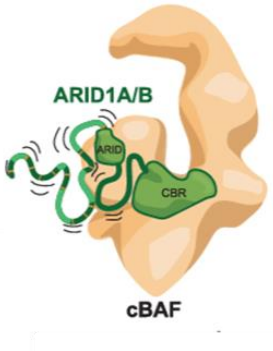

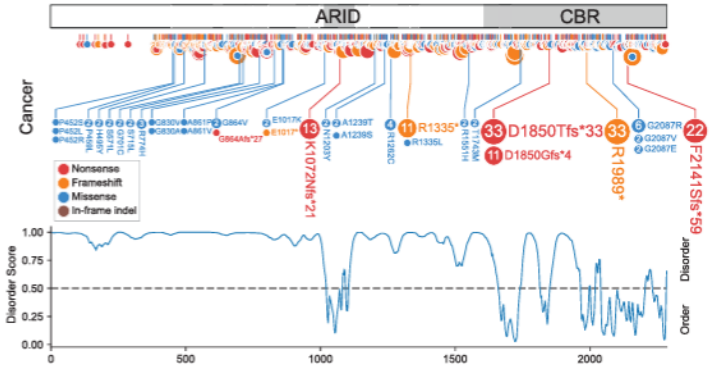

Drugging ARID1B: Challenges and opportunities

- ARID1A/B are mutually exclusive members of the BAF complex
- Nearly two-thirds of the ARID1A/B protein remains uncharacterized due to its highly unstructured nature
- ARID1A is mutated in over 5% of all human cancers arising from a range of cell lineages, representing large unmet need

Why Pursue a Degrader for ARID1B?

- Nothing to inhibit! No known enzymatic function or ligandable domains
- Scaffolding protein connecting the cBAF core with the ATPase module
- High sequence homology (~60%) between the two paralogs – need to engineer selectivity

Patil et al., 2023, Cell 186, 4936–4955

Assessment of ARID1B Suitability for Degradation Approach

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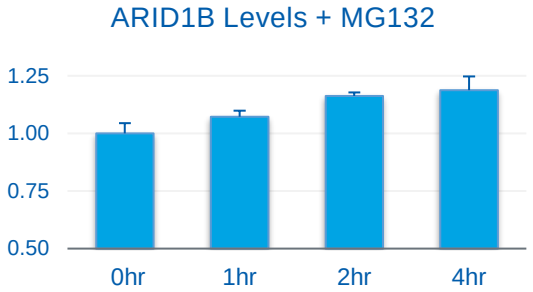
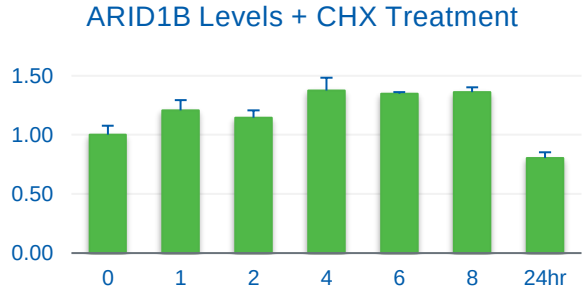
ARID1B IS NATIVELY DEGRADED VIA THE UBIQUITIN-PROTEASOME PATHWAY



ARID1B HAS LONG NATIVE HALF-LIFE



- Endogenous ARID1B is stabilized with proteasome inhibitor (MG132)
- Based upon internal cycloheximide chase experiments and published MS data the **estimated ARID1B native $t_{1/2}$ is 44 - 48 hrs**

Compound Screening and Structure-Based Optimization Yields Selective ARID1B Binders

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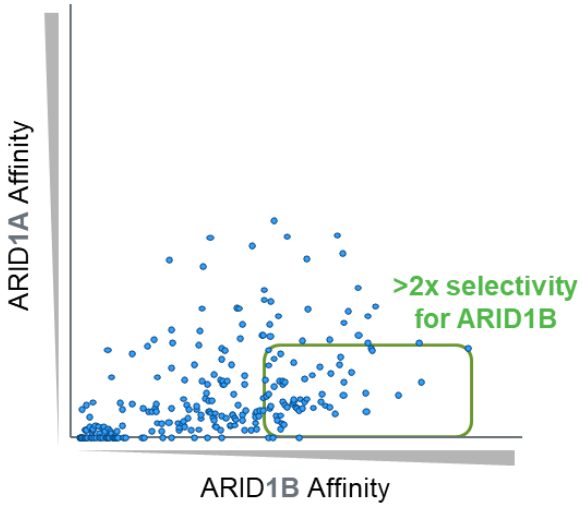
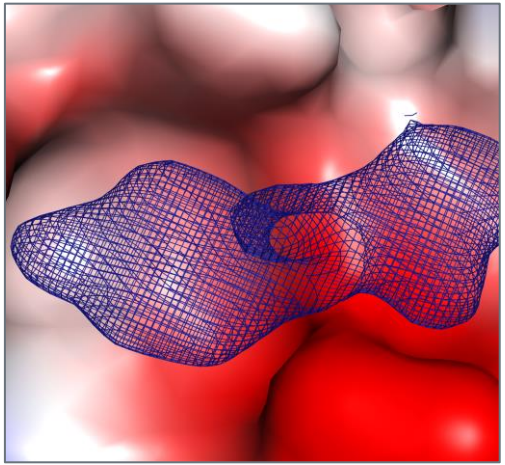
IDENTIFICATION OF SELECTIVE ARID1B BINDERS



- Mapped and purified several potential ligandable regions of ARID, which were then screened against various compound libraries
- Characterized binding using multiple biochemical and biophysical techniques: e.g. DSF, ASMS, NMR, and SPR

X-RAY CRYSTAL STRUCTURES DETAIL SELECTIVE ARID1B BINDING

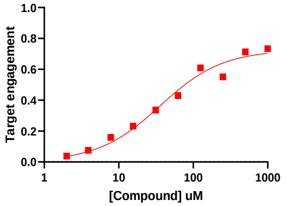


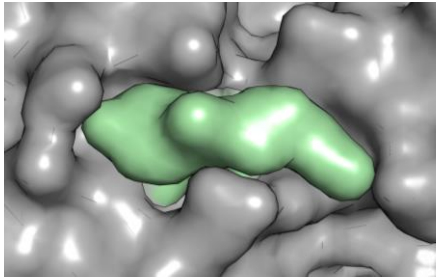
- Determined X-ray crystal structure of ARID ligandable domains with specific binders
- Leveraged these structures to drive binding affinities and expand binding chemotypes

Structure-Based Optimization Drives Improved ARID1B Binding Affinity

GEN 1: SCREENING HIT	GEN 2: EARLY OPTIMIZATION	GEN 3: SUB-UM AFFINITY	

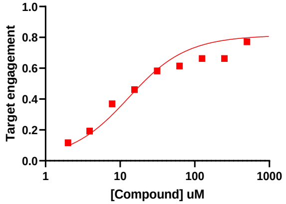
ARIDb-1
ARID1B Kd: **100 uM**

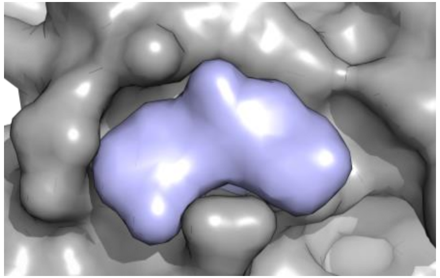




1.4 Å co-xtal structure

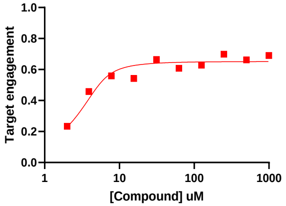
ARIDb-2
ARID1B Kd: **15 uM**

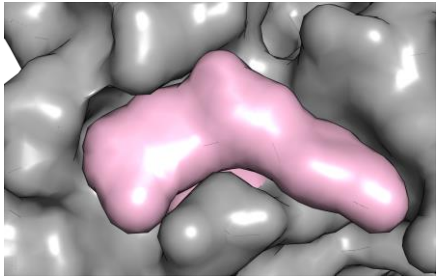




2.0 Å soak structure

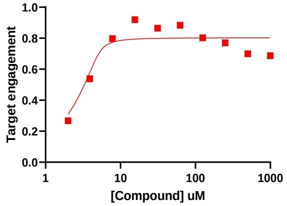
ARIDb-3
ARID1B Kd: **0.5 uM**

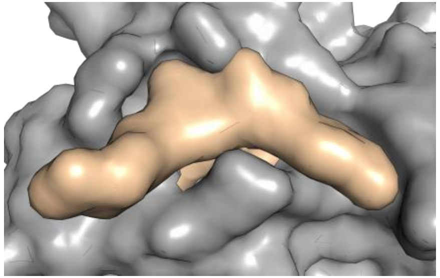




1.9 Å co-xtal structure

ARIDb-9
ARID1B Kd: **0.2 uM**





1.7 Å soak structure

Summary

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- Small molecule inhibitors play an important role in drug discovery and still represent the best path forward for many targets
  - FHD-909 (LY4050784) – a first-in-class selective BRM inhibitor – is entering clinical development
- However, many chromatin regulatory proteins cannot easily be targeted by traditional small molecules:
  - Lack well defined ligandable domains (lacking catalytic, allosteric binding sites)
  - Are structurally dynamic (complex assembly, IDRs)
  - Are scaffolding proteins
- Targeted protein degradation provide an opportunity to overcome many of the challenges that have historically hampered drug discovery for these key oncogenic proteins
- ARID1B is a major synthetic lethal target implicated in ~5% of all cancers
  - Demonstrated suitability for degradation approach
  - Validated selective chemical binders of ARID1B
  - In process of expanding binders into novel selective protein degraders

Acknowledgements

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Check out our other Talks and Posters!

- Symposium SY12: Targeting Chromatin Regulatory Cancer Drivers with Degraders (S. Bellon): Tues morning
- FHD-909 Poster (J. Lee): Mon afternoon; 3230 / 14
- CBP Selective Degrader Poster (D. Sappal): Tues afternoon; 6067 / 26
- EP300 Selective Degrader Poster (M. Zimmerman): Tues afternoon; 6064 / 23
- Long-Acting Injectable Platform Poster (M. Lin): Wed morning; 7185 / 26

Thank you!

Questions?

Disclosure Information

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Laura La Bonte

I have the following relevant financial relationships to disclose:

Employee and stock/option holder of Foghorn Therapeutics Inc.